

(19) World Intellectual Property Organization
International Bureau



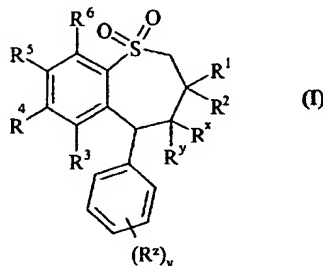
(43) International Publication Date
20 March 2003 (20.03.2003)

PCT

(10) International Publication Number
WO 03/022830 A1

- (51) International Patent Classification⁷: C07D 337/08, 409/12, A61K 31/38, A61P 3/06
- (21) International Application Number: PCT/GB02/04029
- (22) International Filing Date:
5 September 2002 (05.09.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0121622.5 7 September 2001 (07.09.2001) GB
- (71) Applicant (for all designated States except MG, US): **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).
- (71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1Y 6LN (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **STARKE, Ingemar** [SE/SE]; Molndal, S-431 83 (SE). **DAHLSTROM, Mikael, Ulf, Johan** [FI/SE]; Molndal, S-431 83 (SE). **BLOMBERG, David** [SE/SE]; Molndal, S-431 83 (SE).
- (74) Agents: **BRYANT, Tracey et al.**; AstraZeneca, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).
- (81) Designated States (national): AE, AG, AI, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **BENZOTHIPIEPINE ILEAL BILE ACID TRANSPORT INHIBITORS**



(57) Abstract: The present invention relates to compounds of formula (I) wherein variable groups are as defined within; pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

WO 03/022830 A1

BENZOTHIEPINE ILEAL BILE ACID TRANSPORT INHIBITORS

This invention relates to benzothiepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiepinines possess ileal
5 bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a warm-blooded
10 animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*; Circulation
15 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin L, Burke G., *et al*; Circulation, 1999, 100, 1134-46). Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve, for instance, treatment with
20 HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M; Current Opinion on Lipidology, 1999, 10, 269-74) involved the
25 treatment with substances with an IBAT inhibitory effect.

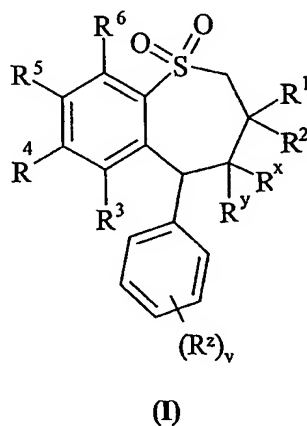
Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties",
30 Biochemica et Biophysica Acta, 1210 (1994) 255- 287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions. Compounds possessing such IBAT inhibitory activity have been described, see for instance hypolipidaemic the compounds described in WO 93/16055, WO 94/18183, WO 94/18184,

WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135,
 WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568,
 WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727,
 WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/50051 and EP 0 864
 5 582.

A further aspect of this invention relates to the use of the compounds of the invention
 in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia,
 hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia
 (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia,
 10 hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In addition, these
 compounds are expected to be useful for the prevention and treatment of different clinical
 conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions,
 vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases,
 cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases,
 15 inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins,
 aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes
 and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical
 trauma and vascular thrombosis, stroke and transient ischaemic attacks.

The present invention is based on the discovery that certain benzothiepine compounds
 20 surprisingly inhibit IBAT. Such properties are expected to be of value in the treatment of
 disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I):



25 wherein:

One of R^1 and R^2 are selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl and the other is selected from C_{1-6} alkyl or C_{2-6} alkenyl;

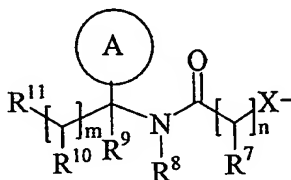
R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkylS(O)_a wherein a is 0 to 2;

R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl,

N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl;

v is 0-5;

one of R^4 and R^5 is a group of formula (IA):



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17} ;

R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ;

R^8 is hydrogen or C_{1-4} alkyl;

R^9 is hydrogen or C_{1-4} alkyl;

p is 1-3; wherein the values of R^{13} may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R^{14} may be the same or different;

m is 0-2; wherein the values of R^{10} may be the same or different;

5 n is 1-3; wherein the values of R^7 may be the same or different;

z is 0-3; wherein the values of R^{25} may be the same or different;

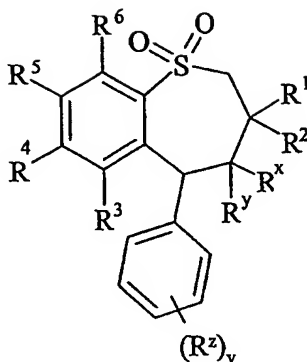
R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ 10 wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl) $_2$ sulphamoyl; wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ;

R^{19} , R^{20} , R^{27} and R^{28} are independently selected from halo, nitro, cyano, hydroxy, 15 amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl, N,N -(C_{1-4} alkyl) $_2$ sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, (C_{1-4} alkyl) $_3$ silyl, phosphono, 20 -P(O)(OR a)(OR b), -P(O)(OH)(OR a), -P(O)(OH)(R a) or -P(O)(OR a)(R b), wherein R a and R b are independently selected from C_{1-6} alkyl; wherein R^{19} and R^{20} may be independently optionally substituted on carbon by one or more R^{22} ;

R^{21} and R^{22} are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, 25 methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N -methylsulphamoyl and N,N -dimethylsulphamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

30 According to a further feature of the present invention there is provided a compound of formula (I):



(I)

wherein:

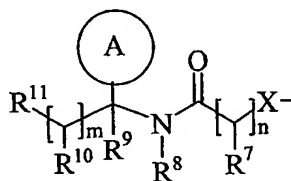
One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected
 5 from C_{1-6} alkyl;

R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto,
 C_{1-6} alkyl, C_{1-6} alkoxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkylS(O) $_a$ wherein a is
 0 to 2;

R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto,
 10 sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy,
 N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl,
 N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-6} alkoxycarbonyl,
 N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;

v is 0-5;

15 one of R^4 and R^5 is a group of formula (IA):



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo,
 nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl,
 20 C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino,
 N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl,
 N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-4} alkoxycarbonyl,

N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

5 **Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17} ;

R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ;

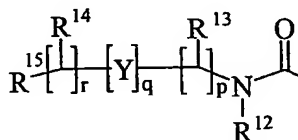
R^8 is hydrogen or C_{1-4} alkyl;

10 R^9 is hydrogen or C_{1-4} alkyl;

R^{10} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^{10} is optionally substituted by one or more substituents selected from R^{19} ;

R^{11} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from

15 C_{1-6} alkyl; or R^{11} is a group of formula (IB):



(IB)

wherein:

20 Y is -N(R^n)-, -N(R^n)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2 and R^n is hydrogen or C_{1-4} alkyl;

R^{12} is hydrogen or C_{1-4} alkyl;

R^{13} and R^{14} are independently selected from hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^{13} and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20} ;

25 R^{15} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^e)(OR^f), -P(O)(OH)(OR^e), -P(O)(OH)(R^f) or -P(O)(OR^e)(R^f) wherein R^e and R^f are independently selected from C_{1-6} alkyl;

p is 1-3; wherein the values of R^{13} may be the same or different;

q is 0-1;

30 r is 0-3; wherein the values of R^{14} may be the same or different;

m is 0-2; wherein the values of **R**¹⁰ may be the same or different;

n is 1-3; wherein the values of **R**⁷ may be the same or different;

R¹⁶, **R**¹⁷ and **R**¹⁸ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, *N*-(C₁₋₄alkyl)amino, *N,N*-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein **a** is 0 to 2, C₁₋₄alkoxycarbonyl, *N*-(C₁₋₄alkyl)sulphamoyl and *N,N*-(C₁₋₄alkyl)₂sulphamoyl; wherein **R**¹⁶, **R**¹⁷ and **R**¹⁸ may be independently optionally substituted on carbon by one or more **R**²¹;

R¹⁹ and **R**²⁰ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, *N*-(C₁₋₄alkyl)amino, *N,N*-(C₁₋₄alkyl)₂amino, C₁₋₄alkanoylamino, *N*-(C₁₋₄alkyl)carbamoyl, *N,N*-(C₁₋₄alkyl)₂carbamoyl, C₁₋₄alkylS(O)_a wherein **a** is 0 to 2, C₁₋₄alkoxycarbonyl, *N*-(C₁₋₄alkyl)sulphamoyl, *N,N*-(C₁₋₄alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein **R**^a and **R**^b are independently selected from C₁₋₆alkyl; wherein **R**¹⁹ and **R**²⁰ may be independently optionally substituted on carbon by one or more **R**²²;

R²¹ and **R**²² are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphanyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C₁₋₆alkyl" includes C₁alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to

other radicals, for example "phenylC₁₋₆alkyl" would include phenylC₁₋₆alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidinonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranlyl, tetrahydrofuranlyl, 2,3-dihydrobenzofuranlyl, benzothienyl, tetrahydropyranlyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino,

1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranlyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

5 A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH₂- group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclopropyl, 10 cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl.

An example of "C₁₋₆alkanoyloxy" and "C₁₋₄alkanoyloxy" is acetoxy. Examples of "C₁₋₆alkoxycarbonyl" and "C₁₋₄alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C₁₋₆alkoxy" and "C₁₋₄alkoxy" include methoxy, ethoxy and propoxy. Examples of "C₁₋₆alkanoylamino" and "C₁₋₄alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C₁₋₆alkylS(O)_a wherein a is 0 to 2" and "C₁₋₄alkylS(O)_a wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C₁₋₆alkanoyl" and "C₁₋₄alkanoyl" 20 include propionyl and acetyl. Examples of "*N*-(C₁₋₆alkyl)amino" and "*N*-(C₁₋₄alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C₁₋₆alkyl)₂amino" and "*N,N*-(C₁₋₄alkyl)₂amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C₂₋₆alkenyl" and "C₂₋₄alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₂₋₆alkynyl" and "C₂₋₄alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C₁₋₆alkyl)sulphamoyl" and "*N*-(C₁₋₄alkyl)sulphamoyl" are 25 *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₆alkyl)₂sulphamoyl" and "*N*-(C₁₋₄alkyl)₂sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₆alkyl)carbamoyl" and "*N*-(C₁₋₄alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of 30 "*N,N*-(C₁₋₆alkyl)₂carbamoyl" and "*N,N*-(C₁₋₄alkyl)₂carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "(C₁₋₄alkyl)₃silyl," include trimethylsilyl and methyldiethylsilyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for

example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention
5 which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

10 The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or
15 hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl;
20 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy
25 group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and
30 *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound of the formula (I) containing a carboxy group is, for example, a *N*-C₁₋₆alkyl or *N,N*-di-C₁₋₆alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess IBAT inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess IBAT inhibitory activity.

Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R¹ and R² are C₁₋₄alkyl.

R¹ and R² are butyl.

One of R¹ and R² is ethyl and the other is butyl.

One of R¹ and R² is ethyl and the other is butyl or R¹ and R² are both butyl.

One of R^x and R^y is hydrogen and the other is hydroxy.

v is 0 or 1.

v is 0.

R^z is C₁₋₄alkyl.

R³ and R⁶ are hydrogen.

R⁴ is methylthio.

R⁴ is hydrogen.

R⁴ is a group of formula (IA) (as depicted above) wherein:

X is -S-;

Ring A is phenyl;

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is a group of formula (IB) (as depicted above) wherein:

R¹² is hydrogen;

p is 1 or 2;

5 R¹³ is hydrogen;

q is 0;

r is 0; and

R¹⁵ is carboxy or sulpho.

10 R⁴ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio or *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio.

R⁴ is a group of formula (IA) (as depicted above) wherein:

X is -S-;

Ring A is phenyl or thienyl; wherein Ring A is optionally substituted by one or more substituents selected from R¹⁷;

15 n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

20 R¹¹ is carboxy or a group of formula (IB) (as depicted above) wherein:

R¹² is hydrogen;

p is 1 or 2;

R¹³ is hydrogen;

q is 0;

25 r is 0;

R¹⁵ is carboxy or sulpho; and

R¹⁷ is hydroxy or fluoro.

R⁴ is a group of formula (IA) (as depicted above) wherein:

X is -S-;

30 Ring A is phenyl, 4-hydroxyphenyl, 2-fluorophenyl or thien-2-yl;

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

R¹¹ is carboxy or a group of formula (IB) (as depicted above) wherein:

5 R¹² is hydrogen;

p is 1 or 2;

R¹³ is hydrogen;

q is 0;

r is 0; and

10 R¹⁵ is carboxy or sulpho.

R⁴ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio; *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio; {*N*-[α -(carboxy)-2-fluorobenzyl]carbamoylmethylthio}; or {*N*-[1-(carboxy)-1-(thien-2-yl)methyl]carbamoylmethylthio}.

15 R⁵ is hydrogen.

R⁵ is a group of formula (IA).

Therefore in another aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein:

R¹ and R² are C₁₋₄alkyl;

20 One of R^x and R^y is hydrogen and the other is hydroxy;

v is 0;

R³ and R⁶ are hydrogen;

R⁴ is a group of formula (IA) (as depicted above) wherein:

X is -S-;

25 Ring A is phenyl or thienyl; wherein Ring A is optionally substituted by one or more substituents selected from R¹⁷;

n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

30 R⁹ is hydrogen;

m is 0;

R¹¹ is carboxy or a group of formula (IB) (as depicted above) wherein:

R¹² is hydrogen;

p is 1 or 2;

R¹³ is hydrogen;

q is 0;

5 r is 0;

R¹⁵ is carboxy or sulpho;

R¹⁷ is hydroxy or fluoro; and

R⁵ is hydrogen;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10 Therefore in another aspect of the invention there is provided a compound of formula

(I) (as depicted above) wherein:

One of R¹ and R² is ethyl and the other is butyl;

One of R^x and R^y is hydrogen and the other is hydroxy;

v is 0;

15 R³ and R⁶ are hydrogen;

R⁴ is *N*-{(R)- α -[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio; *N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio; {*N*-[α -(carboxy)-2-fluorobenzyl]carbamoylmethylthio}; or {*N*-[1-(carboxy)-1-(thien-2-yl)methyl]carbamoylmethylthio}; and

20 R⁵ is hydrogen;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

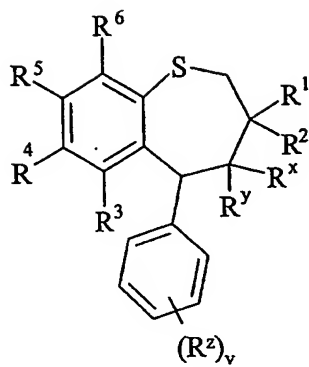
In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

25 Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

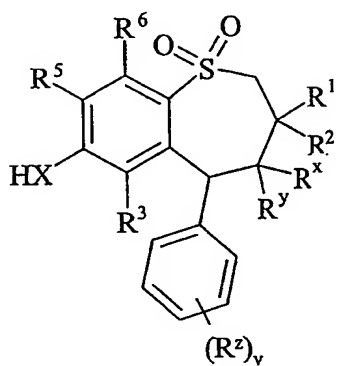
30

Process 1): oxidising a benzothiepine of formula (II):

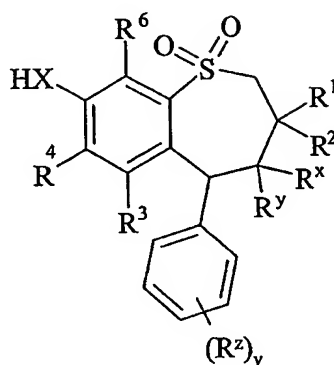


(II);

Process 2): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIIa) or (IIIb):

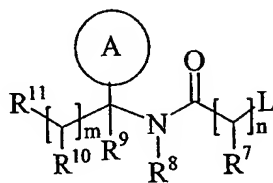


(IIIa)



(IIIb)

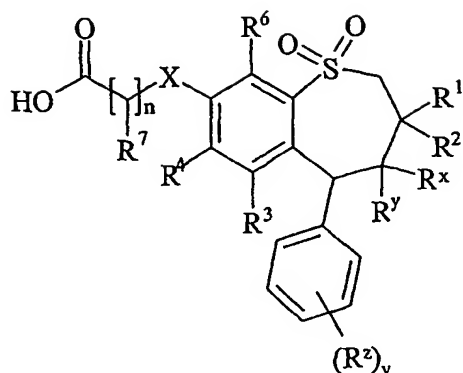
with a compound of formula (IV):



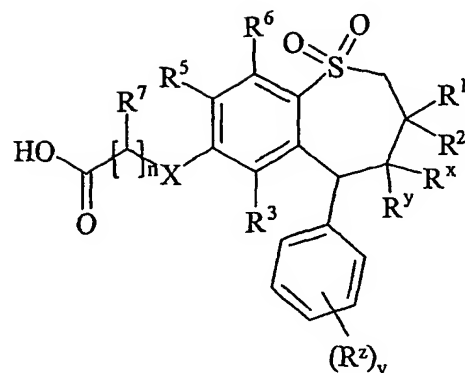
(IV)

10 wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):

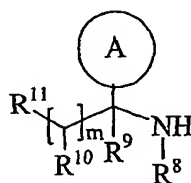


(Va)



(Vb)

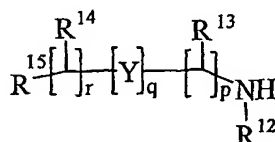
or an activated derivative thereof; with an amine of formula (VI):



(VI);

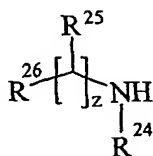
5

Process 4): for compounds of formula (I) wherein R¹¹ is a group of formula (IB); reacting a compound of formula (I) wherein R¹¹ is carboxy with an amine of formula (VII):



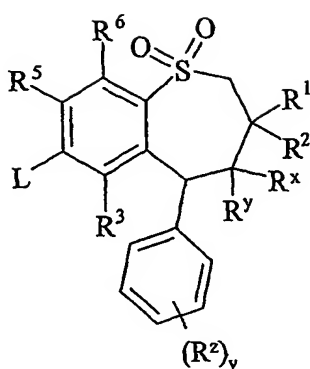
(VII)

10 *Process 5*): for compounds of formula **(I)** wherein R¹¹ is a group of formula **(IB)** and R¹⁵ is a group of formula **(IC)** reacting a compound of formula **(I)** wherein R¹⁵ is carboxy with an amine of formula **(VIII)**:

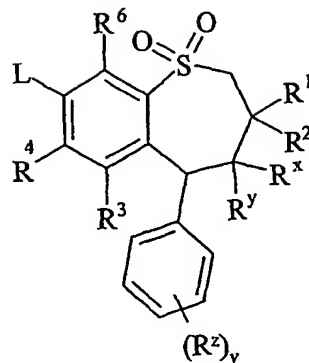


(VIII)

15 *Process 6)* for compounds of formula **(I)** wherein one of R⁴ and R⁵ are independently selected from C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁶, reacting a compound of formula **(IXa)** or **(IXb)**:



(IXa)



(IXb)

wherein L is a displaceable group; with a thiol of formula (X):

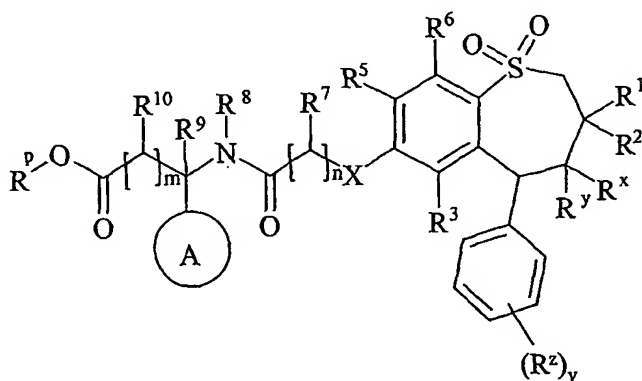


(X)

5

wherein R^m is C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁶;

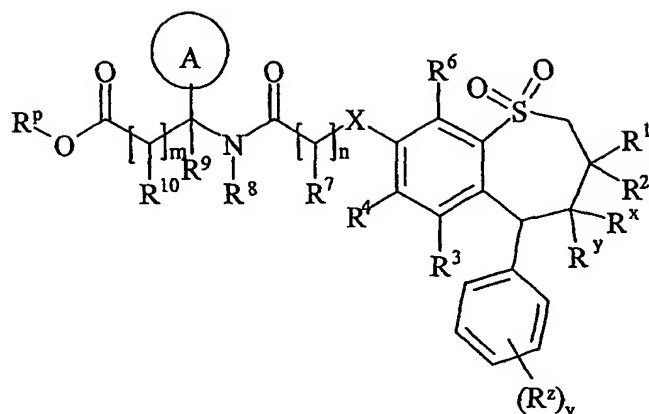
Process 7): for compounds of formula (I) wherein R¹¹ is carboxy; deprotecting a compound of formula (XIa):



(XIa)

10

or (XIb):

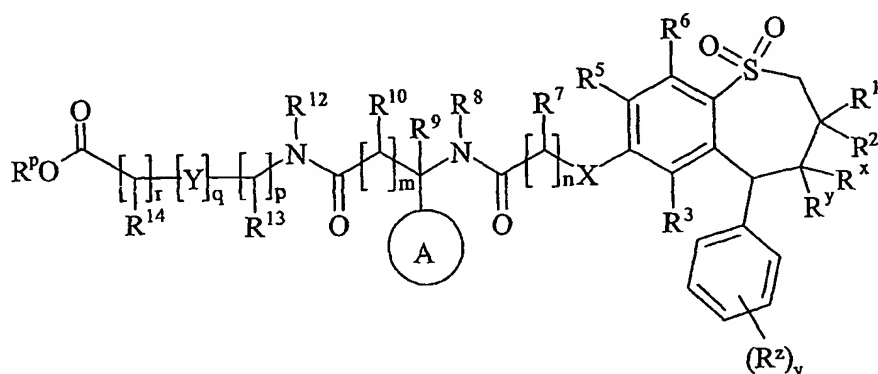


(XIb)

wherein R^p is together with the -OC(O)- group to which it is attached forms an ester;

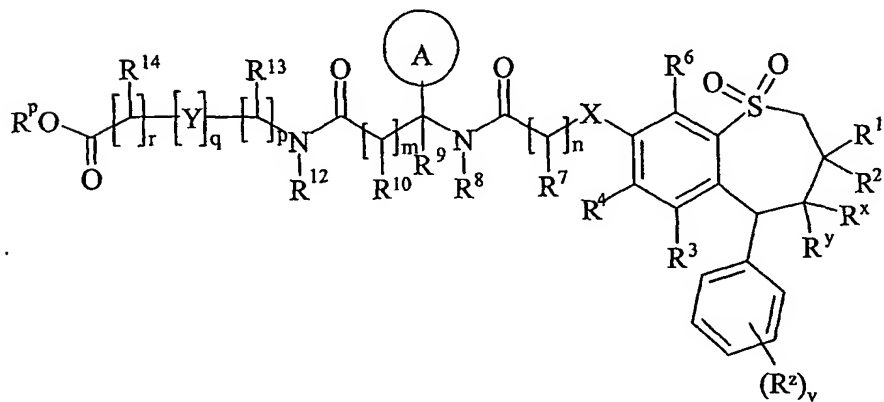
Process 8): for compounds of formula (I) wherein R¹¹ is a group of formula (IB) and R¹⁵ is

5 carboxy; deprotecting a compound of formula (XIIa):



(XIIa)

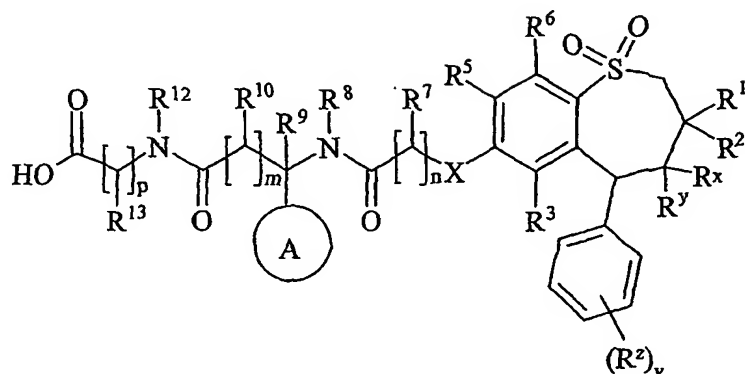
or (XIIb):



(XIIb)

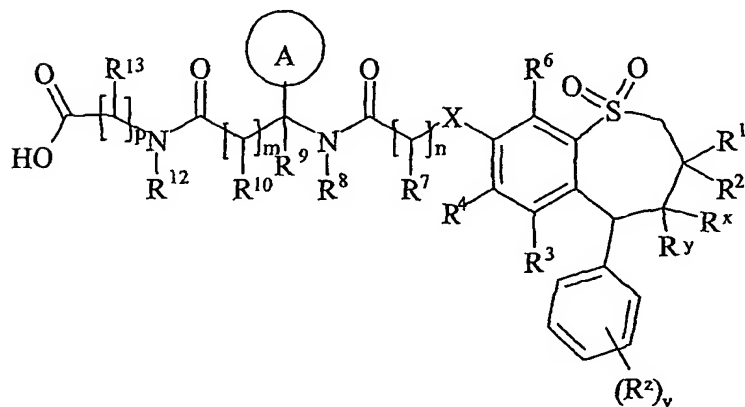
wherein R^p together with the -OC(O)- group to which it is attached forms an ester;

Process 9): for compounds of formula (I) wherein R^{11} is a group of formula (IB) and Y is $-N(R^n)C(O)-$; reacting an acid of formula (XIIIa):



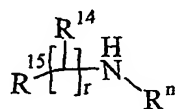
(XIIIa)

5 or (XIIIb):



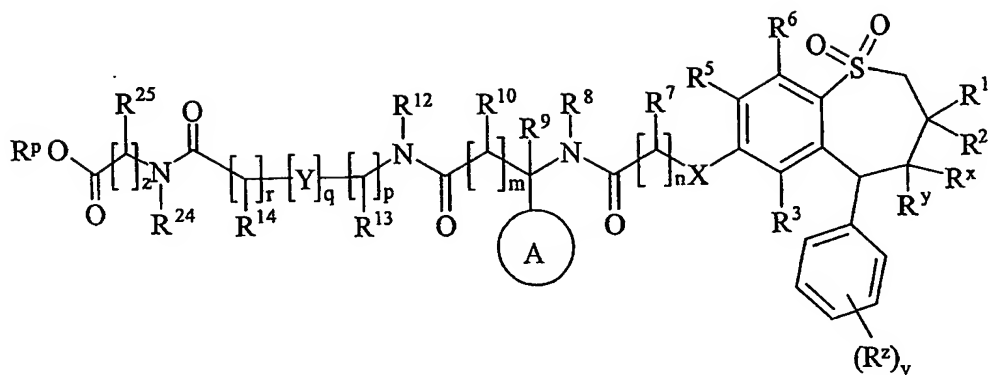
(XIIIb)

or an activated derivative thereof; with an amine of formula (XIV):



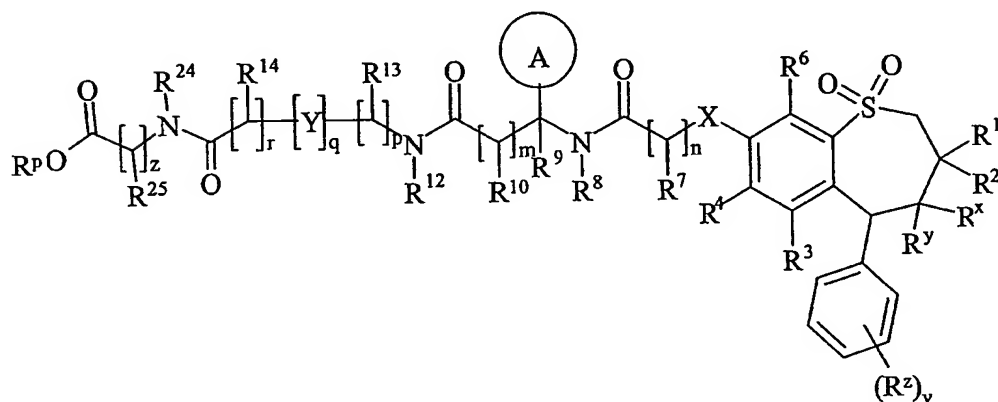
(XIV)

Process 10): for compounds of formula (I) wherein R^{11} is a group of formula (IB), R^{15} is a group of formula (IC) and R^{26} is carboxy; deprotecting a compound of formula (XVa):



(XVa)

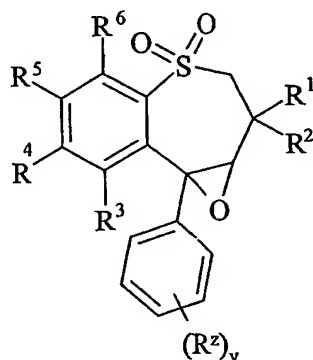
or (XVb):



(XVb)

5

wherein R^p together with the -OC(O)- group to which it is attached forms an ester;
 or *Process 11*) for compounds of formula (I) wherein one of R_x and R_y is hydroxy and the
 other is hydrogen; hydrogenating an epoxide of formula (XVI):



(XVI)

10

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or

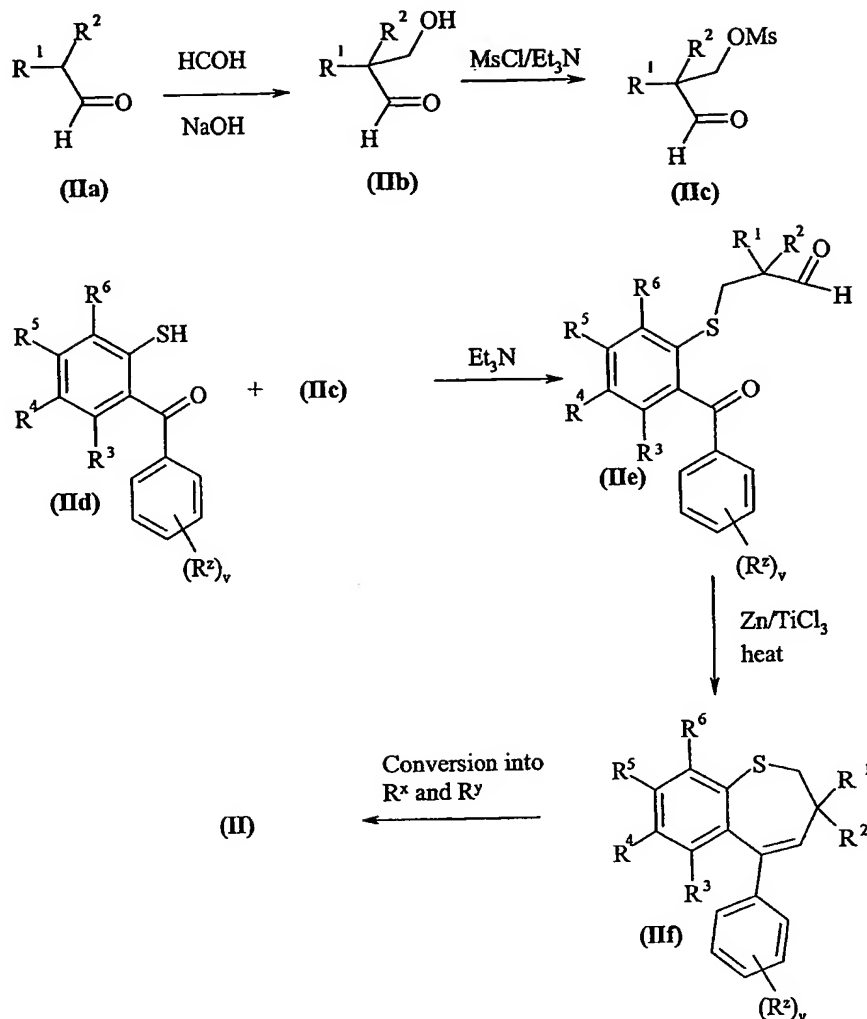
5 toluene-4-sulphonyloxy group.

R^p together with the -OC(O)- group to which it is attached forms an ester. Preferably R^p is methyl or ethyl. More preferably R^p is methyl. In another aspect of the invention R^p is C₁₋₆alkyl or phenylC₁₋₆alkyl, preferably C₁₋₄alkyl or benzyl, more preferably *t*-butyl, methyl, ethyl or benzyl.

10 Specific reaction conditions for the above reactions are as follows.

Process 1): Benzothiepinines of formula (II) may be oxidised under standard sulphur oxidation conditions; for example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

Compounds of formula (II) may be prepared according to Scheme I:



Scheme 1

Compounds of formula (IIa) and (IId) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

- 5 *Process 2*): Compounds of formula (IIIa) or (IIIb) may be reacted with compounds of formula (IV) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

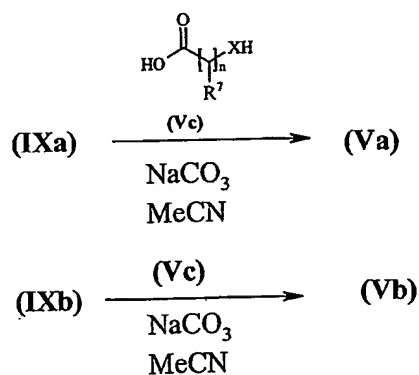
- 10 Compounds of formula (IIIa) or (IIIb) may be prepared in a similar manner to compounds of formula (II) (but wherein R⁴ or R⁵ is -OH, -NH(R^a) or -SH followed by the oxidation step of Process 1). In addition compounds of formula (IIIa) or (IIIb) wherein X is -O- or -NR^a may be prepared by the procedure of WO 96/08484 or WO 98/40375.

Compounds of formula (IV) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 3) and *Process 4)* and *Process 5)* and *Process 9)*: Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Compounds of formula (Va) or (Vb) wherein X=-O-, -NR^a-, -S- may be prepared according to Scheme 2:

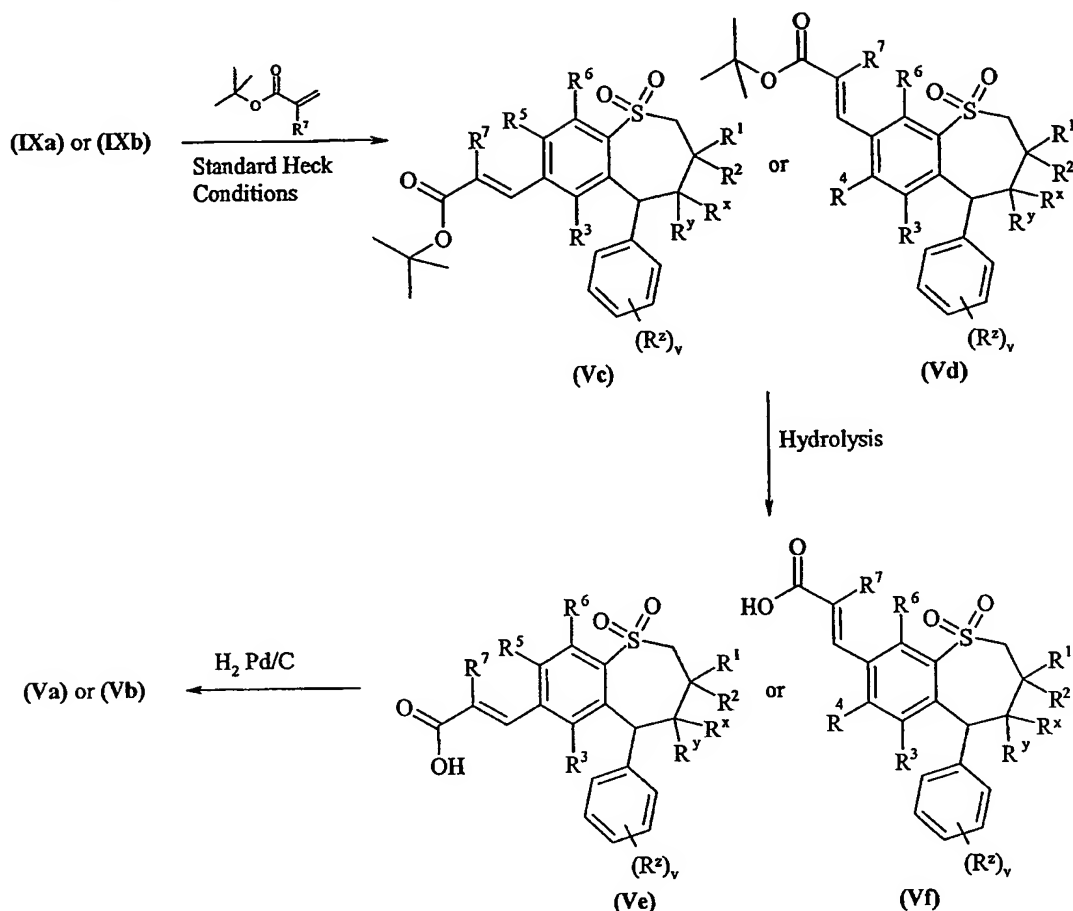


Scheme 2

Wherein L in (IXa) and (IXb) is a displaceable group e.g. bromo, chloro, fluoro, mesyl or tosyl and wherein X is -O-, -S-, NR^a (optionally for -SO- and -SO₂- followed by the oxidation step of Process 1).

Compounds of formula (Va) and (Vb) where X is -SO- or -SO₂- may be prepared by oxidising the resulting compounds of formula (Va) and (Vb) from Scheme 2 where X is -S-.

Compounds of formula (Va) or (Vb) wherein X is $-\text{CH}_2-$, and n is 1, may be prepared according to *Scheme 3*.



Scheme 3

5 The skilled person will appreciate that the above reaction scheme may be manipulated to prepare compounds of formula (Va) or (Vb) where n is 2 or 3.

Compounds of formula (XIIIa) or (XIIIb) may be prepared by manipulations known to the skilled person of the processes described herein.

10 Compounds of formula (Vc), (VI), (VII), (VIII) and (XIV) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 6): Compounds of formula (IXa) and (IXb) may be reacted with thiols of formula (X) in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as Hunigs base, in the presence of a suitable solvent such as DMF or THF at a

15 temperature in the range of 0°C to reflux.

Compounds of formula (IXa) and (IXb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R⁴ and R⁵ is L.

Compounds of formula (X) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

5 *Process 7) and Process 8) and Process 10):* Esters of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb) may be deprotected under standard conditions such as those described below, for example they may be deprotected with sodium hydroxide in methanol at room temperature.

10 Esters of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein R¹¹ or R¹⁵ or R²⁶ is an ester.

Process 11) Compounds of formula (XVI) may be hydrogenated under standard conditions such as in the presence of a palladium catalyst.

15 Compounds of formula (XVI) may be prepared by reacting compounds of formula (III) with excess m-chloroperoxybenzoic acid.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

20
25
30

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed,

for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using
5 conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an *in vitro* test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith L., Price-Jones M. J., Hugnes K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or *in vivo* by
10 studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Brieady L. E. and Root C., J., J Lip Res 1995, 36, 1098-1105).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association
15 with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using
20 conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e.
25 approximately 0.02-100 mg/kg, preferably 0.02 -50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0.1-10 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the
30 severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are effective IBAT inhibitors, and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

Herein, where "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" is referred to particularly this refers to the treatment of hyperlipidaemic conditions. In another aspect, "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In

another aspect "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks. In another aspect "the production of an IBAT inhibitory effect" or "producing an IBAT inhibitory effect" refers to the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The size of the dose required for the therapeutic or prophylactic treatment will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 0.1-50 mg/kg preferably 0.1-10 mg/kg is envisaged.

The IBAT inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, as defined hereinbefore and an additional IBAT inhibitory substance as defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of hyperlipidaemia.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is rosuvastatin calcium salt.

In an additional aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be administered in association with an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate

of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a bile acid binder; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form;
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a bile acid binder, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
5 prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound
10 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound
15 of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
20 prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination
25 treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a
30 prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable excipient, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- a fibric acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;

- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and nicheritrol;
- a phytosterol compound for example stanols;
- probucol;
- 5 ➤ an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic
- 10 blocker, an andrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;
- 15 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in

20 combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril

25 sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphan-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril,

30 spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and

enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041, NN622/Ragaglitazar, BMS 298585 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such

treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable

salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of IBAT in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention. For Example compounds of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb) show IBAT inhibitory activity when tested in the above referenced *in vitro* test assay and are thus claimed as a further feature of the invention.

Thus in a further feature of the invention, there is provided a compound of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

According to an additional aspect of the present invention there is provided a compound of the formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is provided a compound of the formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (XIa), (XIb), (XIIa), (XIIb), (XVa) and (XVb), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

- 5 (i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
- 10 (iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 μm (Merck);
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic
- 15 resonance chemical shift values were measured in deuterated CD_3OD (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt,
- 20 triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; LCMS were recorded on a Waters ZMD, LC column xTerra MS C_8 (Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH^+);
- 25 (vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C_8 , 7 μm , (Akzo Nobel); MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition;
- (vii) intermediates were not generally fully characterised and purity was assessed by thin layer
- 30 chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;
- (viii) where solutions were dried sodium sulphate was the drying agent;

(ix) where an "ISOLUTE" column is referred to, this means a column containing 2g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE";

"ISOLUTE" is a registered trade mark;

5 (x) the following abbreviations may be used hereinbefore or hereinafter:-

DCM	dichloromethane;
DMF	N,N-dimethylformamide;
TBTU	o-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate;
EtOAc	ethyl acetate; and
10 MeCN	acetonitrile.

Example 1

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)- α -[N-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine

15 1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(carboxymethylthio)-2,3,4,5-tetrahydrobenzothiepine (Method 3; 40 mg, 0.086 mmol), (R)- α -[N-(t-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 2; 31 mg, 0.117 mmol) and TBTU (45 mg, 0.140 mmol) were dissolved in DCM (2.5 ml) and 2,6-lutidine (0.03 ml, 0.243 mmol) was added. After stirring at room temperature for 3 hours the reaction mixture was filtered
20 through a short silica column. The crude ester was dissolved in DCM (5 ml) and trifluoroacetic acid (1 ml) was added. After stirring at room temperature over night, the solvents were evaporated and purification with preparative HPLC using MeCN/ammonium acetate buffer (50:50) gave the title compound (26 mg, 46 %). NMR (400 MHz, DMSO-d₆): 0.74 (t, 3H), 0.84 (t, 3H), 1.02 (m, 1H), 1.18-1.46 (m, 5H), 1.60 (m, 1H), 2.01 (m, 1H),
25 3.08/3.15 (ABq, 2H), 3.56-3.85 (m, 4H), 3.94 (s, 1H), 5.23 (d, 1H), 5.48 (d, 1H), 6.43 (dd, 1H), 7.21-7.44 (m, 11H), 7.73 (dd, 1H), 8.47 (brs, 1 H), 8.82 (m, 1H).

Example 2

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)- α -[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine ammonia salt

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(carboxymethylthio)-2,3,4,5-tetrahydrobenzothiepine (Method 3; 50 mg, 0.108 mmol), 2-[[*(2R)*-2-amino-2-(4-hydroxyphenyl)ethanoyl]amino]ethanesulphonic acid (Method 4; 35 mg, 0.127 mmol) and TBTU (45 mg, 0.140 mmol) were dissolved in DMF (2 ml) and *N*-methylmorpholine (0.03 ml, 0.270 mmol) was added. After stirring at ambient temperature for 4 hours the reaction mixture was diluted with MeCN/ammonium acetate buffer (50:50) and purified with preparative HPLC using MeCN/ammonium acetate buffer (50:50) to give the title compound (49 mg, 61 %). NMR (400 MHz, DMSO- d_6): 0.74 (t, 3H), 0.84 (t, 3H), 1.02 (m, 1H), 1.18-1.46 (m, 5H), 1.60 (m, 1H), 2.01 (m, 1H), 3.11 (m, 2H), 3.28 (m, 2H), 3.75 (m, 2H), 3.95 (s, 1H), 5.13 (d, 1H), 5.22 (s, 1H), 6.43 (t, 1H), 6.67 (d, 2H), 7.08 (m, 2H), 7.28-7.44 (m, 9H), 7.76 (m, 1H), 8.16 (m, 1H), 8.68 (dd, 1H).

Example 3

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{*N*-[α -(carboxy)-2-fluorobenzyl]carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(carboxymethylthio)-2,3,4,5-tetrahydrobenzothiepine (Method 3; 59 mg, 0.13 mmol) and methyl amino (2-fluorophenyl)acetate hydrochloride (40 mg, 0.18 mmol) were added to DCM (3.0 ml) and 2,6-lutidine (0.04 ml, 0.38 mmol) was added. The reaction mixture was stirred at ambient temperature for 5 min and TBTU (58 mg, 0.18 mmol) was added. After stirring at ambient temperature for 3 hours the reaction mixture was diluted with DCM (5 ml) and was washed with HCl (aq., 1 M, 5 ml). The DCM layer was separated and evaporated to dryness. The residue was dissolved in THF (2.0 ml) and water (1.0 ml) and NaOH (aq., 1 M, 0.30 mmol) was added. After stirring at ambient temperature for 2 hours the reaction mixture was quenched with HCl (aq., 1 M), diluted with water (10 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were purified with preparative HPLC MeCN/ ammonium acetate buffer 40:60 to give the title compound (70 mg, 89 %). NMR (400 MHz, DMSO- d_6): 0.74 (t, 3H), 0.84 (t, 3H), 1.00 (m, 1H), 1.18-1.46 (m, 5H), 1.60 (m, 1H), 2.02 (m, 1H), 3.11 (m, 2H),

3.69 (m, 2H), 3.94 (s, 1H), 5.04 (t, 1H), 5.23 (d, 1H), 6.44 (d, 1H), 6.94-7.44 (m, 11H), 7.70 (t, 1H), 8.40 (m, 1H).

Example 4

5 **1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{N-[1-(carboxy)-1-(thien-2-yl)methyl]carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine**

The title compound was synthesized according to the procedure of Example 3 but with methyl amino(thien-2-yl)acetate hydrochloride as starting material. NMR (400 MHz, DMSO-
d₆): 0.74 (t, 3H), 0.84 (t, 3H), 1.01 (m, 1H), 1.20-1.47 (m, 5H), 1.60 (m, 1H), 2.01 (m, 1H),
10 3.12 (m, 2H), 3.73 (m, 2H), 3.95 (s, 1H), 5.03 (m, 1H), 5.24 (s, 1H), 6.45 (m, 1H), 6.75 (m, 1H), 6.81 (m, 1H), 7.20 (m, 1H), 7.33 (m, 3H), 7.41 (m, 4H), 7.75 (dd, 1H), 8.32 (dd, 1H).

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are
15 readily prepared by standard Methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

20 **(R)-N-Benzoyloxycarbonyl- α -[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine**

(2R)-{[(Benzyloxy)carbonyl]amino}(phenyl)acetic acid (10 g, 35.0 mmol) and *t*-butylglycine hydrochloride (6.3 g, 37.4 mmol) was dissolved in DCM (200 ml) with 2,6-lutidine (8.2 ml, 70.4 mmol). After stirring 5 min at 0°C TBTU (12.4 g, 38.6 mmol) was added and stirring was continued for 1.5 hours at 0°C and 3.75 hours at room temperature.
25 The reaction mixture was washed with water (2 x 100 ml), dried (MgSO₄) and purified with flash chromatography (DCM:EtOAc 7:1→5:1) to give the title compound (13 g, 94 %). NMR (500 MHz, CDCl₃): 1.45 (s, 9H), 3.84 (d, 1H), 4.00 (dd, 1H), 5.10 (m, 2H), 5.28 (brs, 1H), 6.13 (brs, 1H), 6.23 (brs, 1H), 7.30-7.44 (m, 10H).

Method 2**(R)- α -[N-(*t*-Butoxycarbonylmethyl)carbamoyl]benzylamine**

(R)-*N*-Benzyloxycarbonyl- α -[N-(*t*-butoxycarbonylmethyl)carbamoyl]benzylamine (Method 1; 12.8 g, 32.2 mmol) was dissolved in EtOH (99%, 200 ml) and toluene (50 ml).
5 Pd/C (10%, 0.65 g) was added and hydrogenation was performed at atmospheric pressure for 5.5 hours at room temperature. The reaction mixture was filtered through diatomaceous earth and the solvents were evaporated to give the title compound (8.4 g, 99 %). NMR (600 MHz, CDCl₃): 1.45 (s, 9H), 3.93 (m, 2H), 4.54 (s, 1H), 7.31-7.42 (m, 5H), 7.51 (brs, 1H).

10 Method 3**1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(carboxymethylthio)-2,3,4,5-tetrahydrobenzothiepine**

1,1-Dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-fluoro-2,3,4,5-tetrahydrobenzothiepine (prepared according to WO 98/40375; 300 mg, 0.77 mmol) was
15 dissolved in DMF (3 ml) and caesium carbonate (540 mg, 1.66 mmol) was added followed by ethyl thioglycolate (0.17 ml, 1.54 mmol) and the reaction mixture was subjected to microwave irradiation in a Smith Synthesiser at 100°C for 5 min. The reaction mixture was added to water (25 ml), extracted with DCM (5 x 5 ml) and concentrated. The crude ethyl ester was dissolved in THF (4 ml) and water (2 ml) and NaOH (1 M, 4 ml) was added. The reaction
20 mixture was stirred at ambient temperature for 6 hours, quenched with HCl (1 M), diluted with water (25 ml) and extracted with DCM (4 x 5 ml). The combined organic layers were purified with preparative HPLC using MeCN/ammonium acetate buffer as the eluent (50:50) to give the title compound (172 mg, 48 %). NMR (400 MHz, DMSO-d₆): 0.74 (t, 3H), 0.84 (t, 3H), 1.01 (m, 1H), 1.18-1.46 (m, 5H), 1.60 (m, 1H), 2.02 (m, 1H), 3.07/3.12 (ABq, 2H),
25 3.33/3.39 (ABq, 2H), 3.95 (s, 1H), 5.23 (s, 1H), 6.38 (d, 1H), 7.19 (dd, 1H), 7.34 (m, 1H), 7.42 (m, 4H), 7.73 (d, 1H).

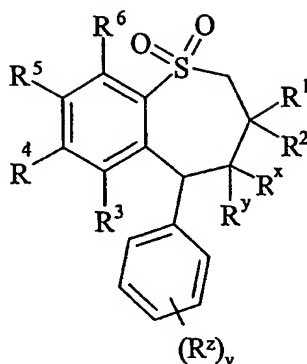
Method 4**2-[[[(2R)-2-Amino-2-(4-hydroxyphenyl)ethanoyl]amino]ethanesulphonic acid**

N-Boc-4-hydroxyphenylglycine (1.00 g, 3.21 mmol) was dissolved in DMF (5 ml) and tetrabutylammonium taurine (2.36 g, 6.42 mmol) was added together with additionally 5 ml
5 DMF. The resulting suspension was cooled on ice and TBTU (1.24 g, 3.85 mmol) was added. The ice bath was removed after 30 min and the mixture was stirred for 2 hours before it was filtered and concentrated. TFA in DCM (20%, 20 ml) was added and the reaction mixture was stirred over night. Ethanol (20 ml) was added and the solvents evaporated. The crude product was refluxed in ethanol (100 ml) for 1 hour. Filtration yielded the pure title compound as a
10 white solid, 626 mg (71%). NMR (DMSO- d_6): 2.4-2.6 (m, 2H), 3.2-3.4 (m, 2H), 4.79 (s, 1H), 6.78 (d, 2H), 7.23 (d, 2H), 8.22 (t, 1H), 8.4 (brs, 3H), 9.7 (s, 1H).

Claims

What we claim is:

1. A compound of formula (I):



(I)

wherein:

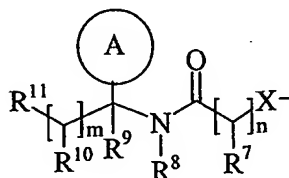
- One of R^1 and R^2 are selected from hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl and the other is selected from C_{1-6} alkyl or C_{2-6} alkenyl;

R^x and R^y are independently selected from hydrogen, hydroxy, amino, mercapto, C_{1-6} alkyl, C_{1-6} alkoxy, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2;

- R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, $C_{1-6}alkanoyl$, $C_{1-6}alkanoyloxy$, $N-(C_{1-6}alkyl)amino$, $N,N-(C_{1-6}alkyl)_2amino$, $C_{1-6}alkanoylamino$, $N-(C_{1-6}alkyl)carbamoyl$, $N,N-(C_{1-6}alkyl)_2carbamoyl$, $C_{1-6}alkylS(O)_a$ wherein a is 0 to 2, $C_{1-6}alkoxycarbonyl$, $N-(C_{1-6}alkyl)sulphamoyl$ and $N,N-(C_{1-6}alkyl)_2sulphamoyl$;

v is 0-5;

- one of R^4 and R^5 is a group of formula (IA):



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl)₂amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl)₂carbamoyl, C_{1-4} alkylS(O)_a wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{16} ;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

10 **Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from R^{17} ;

R^7 is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted by one or more substituents selected from R^{18} ;

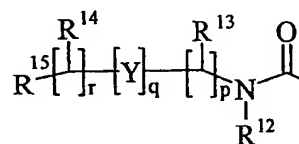
R^8 is hydrogen or C_{1-4} alkyl;

15 R^9 is hydrogen or C_{1-4} alkyl;

R^{10} is hydrogen, C_{1-4} alkyl, carbocyclyl or heterocyclyl; wherein R^{10} is optionally substituted by one or more substituents selected from R^{19} ;

R^{11} is carboxy, sulpho, sulphino, phosphono, -P(O)(OR^c)(OR^d), -P(O)(OH)(OR^c), -P(O)(OH)(R^d) or -P(O)(OR^c)(R^d) wherein R^c and R^d are independently selected from

20 C_{1-6} alkyl; or R^{11} is a group of formula (IB):



(IB)

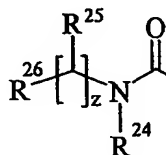
wherein:

Y is -N(R^n)-, -N(R^n)C(O)-, -O-, and -S(O)_a-; wherein a is 0-2 and R^n is hydrogen or C_{1-4} alkyl;

R^{12} is hydrogen or C_{1-4} alkyl;

R^{13} and R^{14} are independently selected from hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl; wherein R^{13} and R^{14} may be independently optionally substituted by one or more substituents selected from R^{20} ;

R^{15} is carboxy, sulpho, sulphino, phosphono, $-P(O)(OR^e)(OR^f)$, $-P(O)(OH)(OR^e)$, $-P(O)(OH)(R^e)$ or $-P(O)(OR^e)(R^f)$ wherein R^e and R^f are independently selected from C_{1-6} alkyl; or R^{15} is a group of formula (IC):



(IC)

wherein:

R^{24} is selected from hydrogen or C_{1-4} alkyl;

R^{25} is selected from hydrogen, C_{1-4} alkyl, carbocyclyl, heterocyclyl or R^{27} ; wherein said C_{1-4} alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from R^{28} ;

R^{26} is selected from carboxy, sulpho, sulphino, phosphono, tetrazolyl, $-P(O)(OR^g)(OR^h)$, $-P(O)(OH)(OR^g)$, $-P(O)(OH)(R^g)$ or $-P(O)(OR^g)(R^h)$ wherein R^g and R^h are independently selected from C_{1-6} alkyl;

p is 1-3; wherein the values of R^{13} may be the same or different;

q is 0-1;

r is 0-3; wherein the values of R^{14} may be the same or different;

m is 0-2; wherein the values of R^{10} may be the same or different;

n is 1-3; wherein the values of R^7 may be the same or different;

z is 0-3; wherein the values of R^{25} may be the same or different;

R^{16} , R^{17} and R^{18} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-4} alkoxycarbonyl, N -(C_{1-4} alkyl)sulphamoyl and N,N -(C_{1-4} alkyl) $_2$ sulphamoyl; wherein R^{16} , R^{17} and R^{18} may be independently optionally substituted on carbon by one or more R^{21} ;

R^{19} , R^{20} , R^{27} and R^{28} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N -(C_{1-4} alkyl)amino, N,N -(C_{1-4} alkyl) $_2$ amino, C_{1-4} alkanoylamino, N -(C_{1-4} alkyl)carbamoyl, N,N -(C_{1-4} alkyl) $_2$ carbamoyl, C_{1-4} alkylS(O) $_a$

wherein a is 0 to 2, C₁₋₄alkoxycarbonyl, *N*-(C₁₋₄alkyl)sulphamoyl, *N,N*-(C₁₋₄alkyl)₂sulphamoyl, carbocyclyl, heterocyclyl, sulphy, sulphino, amidino, (C₁₋₄alkyl)₃silyl, phosphono, -P(O)(OR^a)(OR^b), -P(O)(OH)(OR^a), -P(O)(OH)(R^a) or -P(O)(OR^a)(R^b), wherein R^a and R^b are independently selected from C₁₋₆alkyl; wherein R¹⁹ and R²⁰ may be independently optionally substituted on carbon by one or more R²²;

R²¹ and R²² are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphanyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

2. A compound of formula (I) as claimed in claim 1 wherein one of R¹ and R² is ethyl and the other is butyl or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

3. A compound of formula (I) as claimed in either of claims 1 or 2 wherein one of R^x and R^y is hydrogen and the other is hydroxy or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

4. A compound of formula (I) as claimed in any one of claims 1-3 wherein v is 0 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

5. A compound of formula (I) as claimed in any one of claims 1-4 wherein R³ and R⁶ are hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

6. A compound of formula (I) as claimed in any one of claims 1-5 wherein R⁴ is a group of formula (IA) (as depicted above) wherein:

X is -S-;

Ring A is phenyl or thienyl; wherein Ring A is optionally substituted by one or more substituents selected from R¹⁷;

- n is 1;
R⁷ is hydrogen;
5 R⁸ is hydrogen;
R⁹ is hydrogen;
m is 0;
R¹¹ is carboxy or a group of formula (IB) (as depicted above) wherein:
R¹² is hydrogen;
10 p is 1 or 2;
R¹³ is hydrogen;
q is 0;
r is 0;
R¹⁵ is carboxy or sulpho; and
15 R¹⁷ is hydroxy or fluoro;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

7. A compound of formula (I) as claimed in any one of claims 1-6 wherein R⁵ is
20 hydrogen or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

8. A compound of formula (I) (as depicted in claim 1) wherein:
R¹ and R² are C₁₋₄alkyl;
25 One of R^x and R^y is hydrogen and the other is hydroxy;
v is 0;
R³ and R⁶ are hydrogen;
R⁴ is a group of formula (IA) (as depicted above) wherein:
X is -S-;
30 Ring A is phenyl or thienyl; wherein Ring A is optionally substituted by one or more substituents selected from R¹⁷;
n is 1;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

m is 0;

5 R¹¹ is carboxy or a group of formula (IB) (as depicted above) wherein:

R¹² is hydrogen;

p is 1 or 2;

R¹³ is hydrogen;

q is 0;

10 r is 0;

R¹⁵ is carboxy or sulpho;

R¹⁷ is hydroxy or fluoro; and

R⁵ is hydrogen;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

15

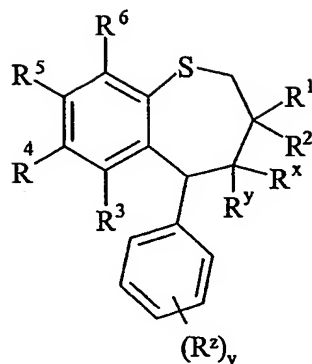
9. A compound of formula (I), as depicted in claim 1, selected from:

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)-α-[N-(carboxymethyl)carbamoyl]benzyl} carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine
1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(N-{(R)-α-[N-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl} carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine ammonia salt
20 1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{N-[α-(carboxy)-2-fluorobenzyl] carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine; and
1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{N-[1-(carboxy)-1-(thien-2-yl)methyl] carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine

25 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

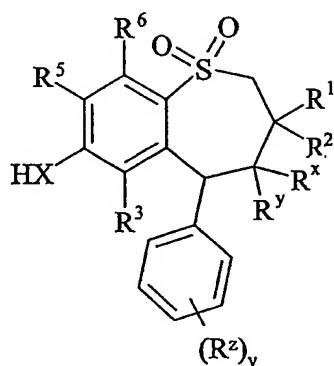
10. A process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1-9, which process comprises of:

30 *Process 1*): oxidising a benzothiepine of formula (II):

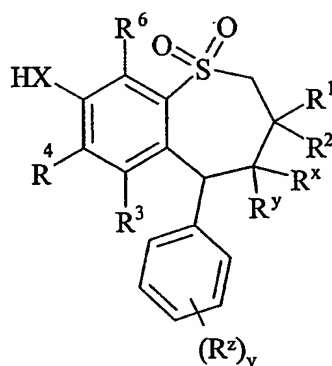


(II);

Process 2): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIIa) or (IIIb):

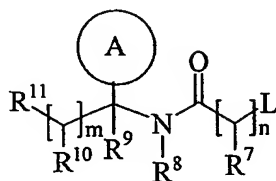


(IIIa)



(IIIb)

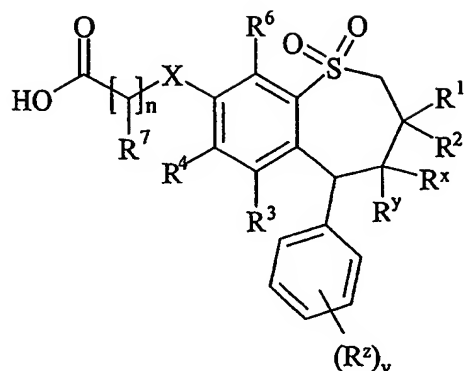
with a compound of formula (IV):



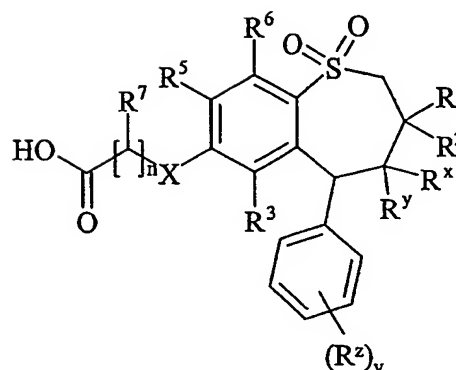
(IV)

10 wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):

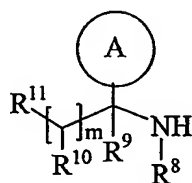


(Va)



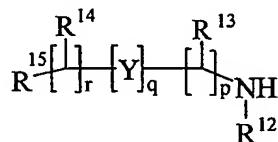
(Vb)

or an activated derivative thereof; with an amine of formula (VI):



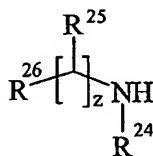
(VI);

Process 4): for compounds of formula (I) wherein R¹¹ is a group of formula (IB); reacting a compound of formula (I) wherein R¹¹ is carboxy with an amine of formula (VII):



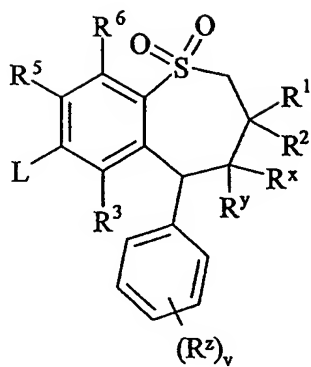
(VII)

- 10 *Process 5):* for compounds of formula (I) wherein R¹¹ is a group of formula (IB) and R¹⁵ is a group of formula (IC) reacting a compound of formula (I) wherein R¹⁵ is carboxy with an amine of formula (VIII):

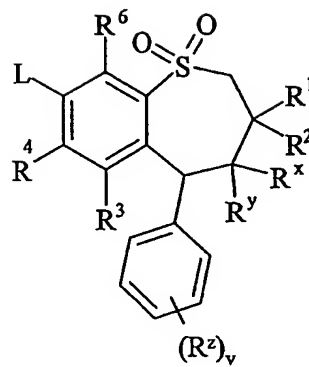


(VIII)

- 15 *Process 6)* for compounds of formula (I) wherein one of R⁴ and R⁵ are independently selected from C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁶; reacting a compound of formula (IXa) or (IXb):



(IXa)



(IXb)

wherein L is a displaceable group; with a thiol of formula (X):

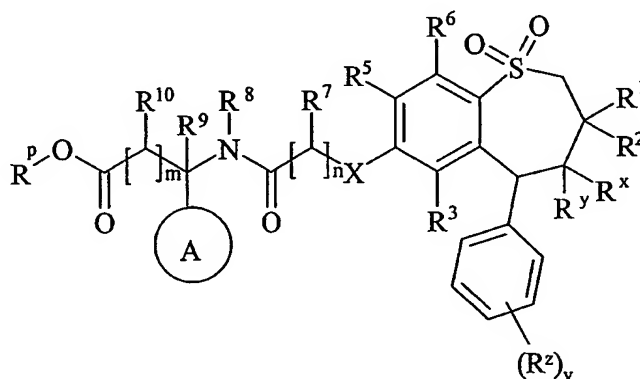


(X)

5

wherein R^m is C₁₋₆alkylthio optionally substituted on carbon by one or more R¹⁶;

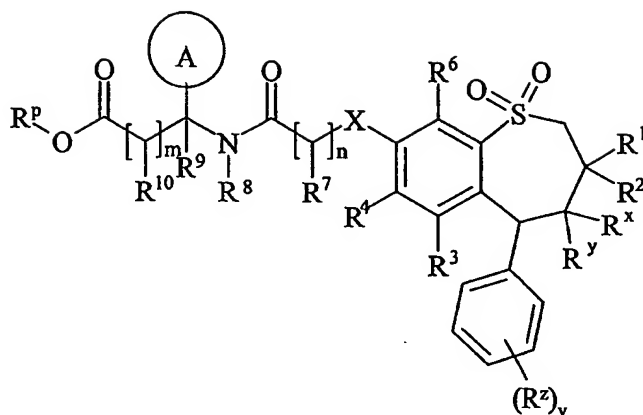
Process 7): for compounds of formula (I) wherein R¹¹ is carboxy; deprotecting a compound of formula (XIa):



(XIa)

10

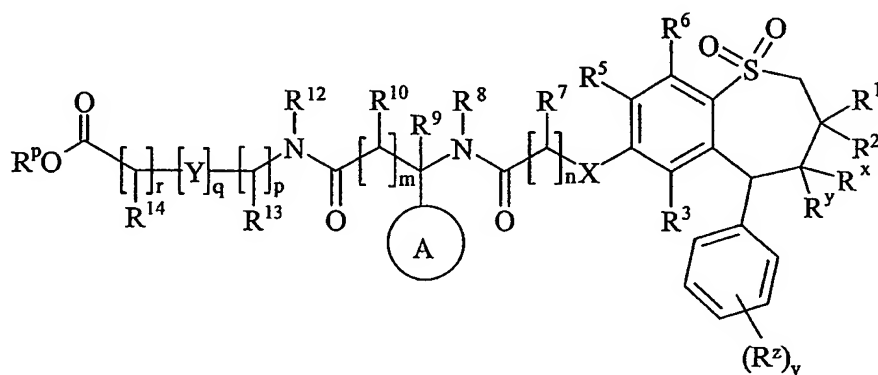
or (XIb):



(XIb)

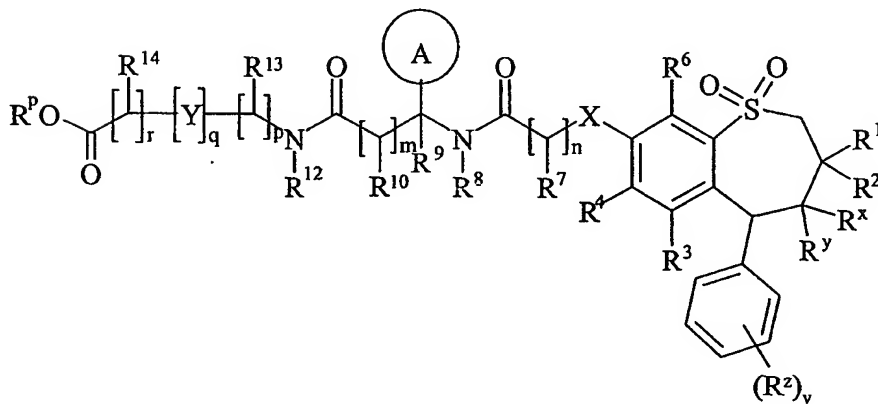
wherein R^p is together with the -OC(O)- group to which it is attached forms an ester;

Process 8): for compounds of formula (I) wherein R¹¹ is a group of formula (IB) and R¹⁵ is
5 carboxy; deprotecting a compound of formula (XIIa):



(XIIa)

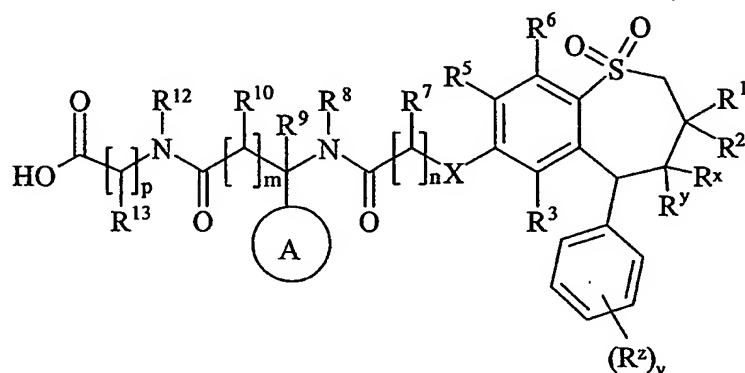
or (XIIb):



(XIIb)

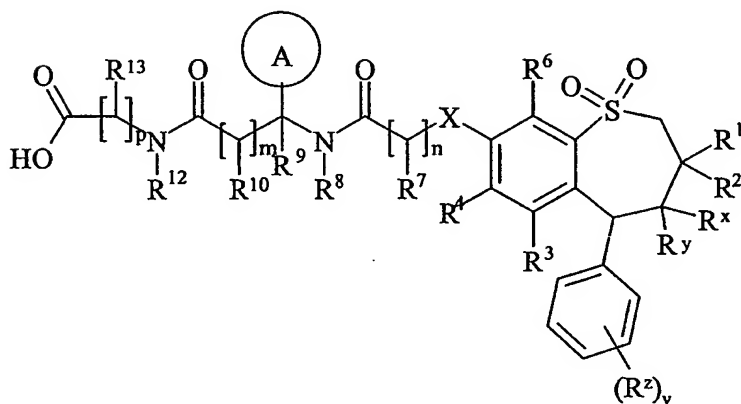
wherein R^p together with the -OC(O)- group to which it is attached forms an ester;

Process 9): for compounds of formula (I) wherein R^{11} is a group of formula (IB) and Y is $-N(R^n)C(O)-$; reacting an acid of formula (XIIIa):



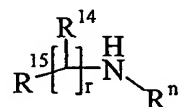
(XIIIa)

5 or (XIIIb):



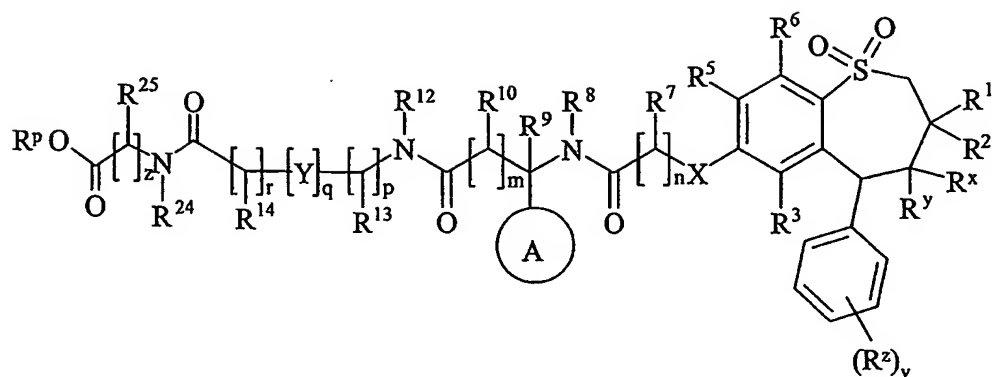
(XIIIb)

or an activated derivative thereof; with an amine of formula (XIV):



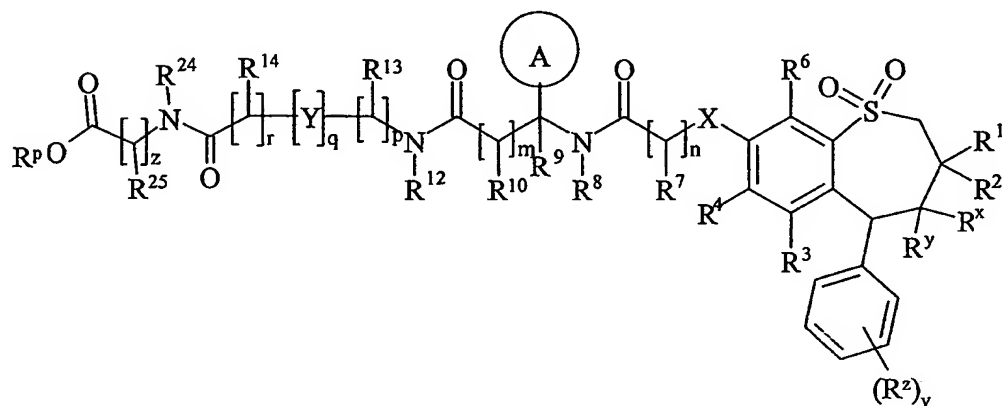
(XIV)

Process 10): for compounds of formula (I) wherein R^{11} is a group of formula (IB), R^{15} is a group of formula (IC) and R^{26} is carboxy; deprotecting a compound of formula (XVa):



(XVa)

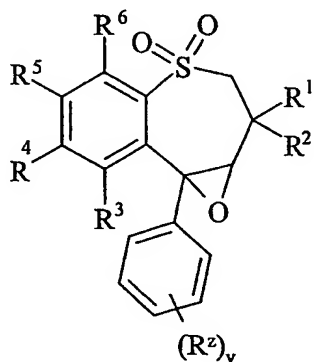
or (XVb):



(XVb)

5

wherein R^p together with the $-OC(O)-$ group to which it is attached forms an ester;
or *Process 11*) for compounds of formula (I) wherein one of R_x and R_y is hydroxy and the other is hydrogen; hydrogenating an epoxide of formula (XVI):



(XVI)

10

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

11. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9 for use as a medicament.

12. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

13. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

14. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

15. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9.

16. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9, in association with a pharmaceutically-acceptable diluent or carrier.

17. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as

claimed in any one of claims 1 to 9, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

- 5 18. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.
- 10 19. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 9, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.
- 15 20. A composition according to claim 17 or claim 19 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 20 21. A composition according to claim 17 or claim 19 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.
22. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as
25 claimed in any one of claims 1 to 9 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.
23. A composition according to claim 22 wherein the PPAR alpha and/or gamma agonist
30 is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/04029

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D337/08 C07D409/12 A61K31/38 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 40375 A (GLENN KEVIN C ;LEE LEN F (US); REITZ DAVID B (US); SEARLE & CO (US) 17 September 1998 (1998-09-17) scheme 6, formula XXIX examples 64,71	1-23
A	WO 96 08484 A (MONSANTO CO ;LEE LEN FANG (US); MILLER RAYMOND EUGENE (US); TREMON) 21 March 1996 (1996-03-21) scheme 6, formula XXIX examples 23,33; table 1	1-23
P,A	WO 02 50051 A (ASTRAZENECA UK LTD ;ASTRAZENECA AB (SE); BLOMBERG DAVID (SE); STAR) 27 June 2002 (2002-06-27) claim 1; examples	1-23

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

11 December 2002

Date of mailing of the international search report

18/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/04029

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15 and 15 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/GB 02/04029

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9840375	A	17-09-1998	AU 730024 B2	22-02-2001
			AU 6440898 A	29-09-1998
			BG 103793 A	31-07-2000
			BR 9808013 A	25-09-2001
			CN 1255864 T	07-06-2000
			EP 0971744 A2	19-01-2000
			HU 0002395 A2	28-05-2001
			JP 2002500628 T	08-01-2002
			NO 994390 A	04-11-1999
			NZ 337830 A	27-07-2001
			PL 336415 A1	19-06-2000
			SK 125099 A3	12-02-2001
			US 6268392 B1	31-07-2001
			WO 9840375 A2	17-09-1998
			US 6420417 B1	16-07-2002
WO 9608484	A	21-03-1996	AT 199718 T	15-03-2001
			AU 700557 B2	07-01-1999
			AU 3373695 A	29-03-1996
			BR 9508916 A	30-12-1997
			CA 2199944 A1	21-03-1996
			CN 1162311 A ,B	15-10-1997
			DE 69520364 D1	19-04-2001
			DE 69520364 T2	13-09-2001
			DK 781278 T3	17-04-2001
			EP 0781278 A1	02-07-1997
			ES 2155136 T3	01-05-2001
			GR 3035583 T3	29-06-2001
			JP 10505830 T	09-06-1998
			JP 3304093 B2	22-07-2002
			PT 781278 T	30-08-2001
			US 6268392 B1	31-07-2001
			WO 9608484 A1	21-03-1996
			US 5994391 A	30-11-1999
			US 6107494 A	22-08-2000
			US 6262277 B1	17-07-2001
			US 6420417 B1	16-07-2002
			US 2002013476 A1	31-01-2002
WO 0250051	A	27-06-2002	AU 2222802 A	01-07-2002
			WO 0250051 A1	27-06-2002